REMARKS/ARGUMENTS

As a preliminary matter, Applicants note that the Examiner states that copies of some of the references listed in the Information Disclosure Statement filed September 16, 2004 were not received and therefore have not been considered. Applicants file herewith a Supplemental Information Disclosure Statement (IDS) re-citing these references and providing copies of same. Applicants respectfully request that the Examiner enter this Supplemental IDS into the application.

Claims 1, 6, 29, and 30 have been amended, claim 41 has been added, and claims 2, 11, 13-28, 31-35, and 37-40 have been cancelled without prejudice to or disclaimer of the subject matter encompassed thereby in order to further prosecution of this application. Applicants expressly reserve the right to file continuing applications or take other such appropriate measures to seek protection for the inventions encompassed by the cancelled subject matter.

Claims 1 and 6 have been amended to reflect the species elected in Applicants' Response dated November 2, 2004, namely the species "overactive bladder" within the group of urinary tract disorders, "orally" within the group of methods of administration, and "ziconotide" (ω-conotoxin MVIIA), within the group of Cav2.2 calcium channel modulators. Claim 41 has been added to reflect Applicants' election of "ω-conotoxin GVIA" within the group of additional active agents, and corresponds to original claim 36. Claims 29 and 30 have been amended to further clarify types of overactive bladder that may be treated according to the methods of the present invention, support for which may be found throughout the specification but particularly on page 6, lines 27-29 and page 17, lines 14-23. Accordingly, no new matter has been added by way of amendment or the addition of claims.

Claims 1, 3-10, 12, 29-30, 36, and 41 are pending in the application. Reexamination and reconsideration of the claims are respectfully requested in view of the claim amendments and the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

Election of Species

Applicants thank the Examiner for acknowledging Applicants' election of "overactive bladder" within the group of urinary tract disorders, "orally" within the group of methods of administration, and "ziconotide" within the group of Cav2.2 calcium channel modulators (see Office Action dated August 30, 2005, page 2, first paragraph). However, Applicants wish to clarify several points on the record with respect to the election made in Applicants' Response dated November 2, 2004.

First, the Examiner states that Applicants elected "ω-conotoxin" from within the group of additional active agents (see Office Action dated August 30, 2005, page 2, first paragraph). However, as described on page 1 of Applicants' Response dated November 2, 2004, Applicants elected ω-conotoxin GVIA from the group of additional active agents.

Second, the Examiner states that "In the instant case, applicants have elected ω-conotoxin GVIA and the synthetic equivalent ziconotide" (see Office Action dated August 30, 2005, page 4, second full paragraph). Although the Examiner implicitly acknowledges Applicants' argument made in connection with the election of ziconotide regarding its synthetic equivalence to a ω-conotoxin, Applicants wish to point out that ziconotide is the synthetic equivalent of ω-conotoxin MVIIA, not ω-conotoxin GVIA (as described on page 2 of Applicants' Response dated November 2, 2004). Applicants' election of ω-conotoxin GVIA was in connection with the group of additional active agents, as described above.

The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

The Examiner has rejected claims 1-40 as being unpatentable over Maggi *et al.* (1988) *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 338:107-113 in view of Yoshimura *et al.* (2001) *J. Neurophysiol.*, 86:304-311. Claims 2, 11, 13-28, 31-35, and 37-40 have been cancelled. This rejection is traversed with respect to the remaining and newly added claims.

The pending claims are drawn to the treatment of overactive bladder via oral administration of ziconotide (ω-conotoxin MVIIA). As a preliminary matter, Applicants note that neither Maggi *et al.* nor Yoshimura *et al.* disclose ω-conotoxin MVIIA or its synthetic

equivalent ziconotide. As described above regarding Applicants' election of species, the Examiner appears to have mistaken ω-conotoxin GVIA as the synthetic equivalent ziconotide, and has cited Maggi *et al.* and Yoshimura *et al.* on that basis. However, to the extent that ω-conotoxin MVIIA and ω-conotoxin GVIA are both ω-conotoxins and are structurally and functionally related, Applicants will address the Examiner's rejection based upon the teachings of the cited references with respect to ω-conotoxins generally.

Any rejection for obviousness requires, among other things, there must also be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The motivation to combine or modify the references must be found in the prior art itself, not in Applicants' disclosure. *In re Dow Chemical*, 837. F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). It is Applicants' contention that there is no motivation to combine the Maggi *et al.* and Yoshimura *et al.* references with respect to treatments for overactive bladder.

The Maggi *et al.* reference describes a study in which the effects of ω-conotoxin GVIA on the contractile properties of isolated strips of bladder smooth muscle via Ca^{+2} channels in the nerve terminals of bladder afferents were measured. The Yoshimura *et al.* reference describes a study of the effect of nitric oxide (NO) on Ca^{+2} channels in dorsal root ganglion neurons innervating rat urinary bladder showing that ω-conotoxin GVIA acts on the same calcium channels as NO, and refers to the use of orally administered L-arginine, an NO precursor as an effective treatment for interstitial cystitis. The Examiner states that it would have been obvious to one of skill in the art to use ω-conotoxin instead of NO or an NO precursor in order to obtain the desired effect of blocking Ca^{+2} channels to treat lower urinary tract disorders.

It is well known in the art that interstitial cystitis is a painful inflammation of the bladder without evidence of infection that is typically treated with drugs aimed at ameliorating the inflammatory process such as antibiotics. By contrast, overactive bladder is characterized by overactivity of the detrusor muscle (see the specification of the present application, page 15, lines 6 to 12) and has traditionally been treated with drugs such as antimuscarinics. Due to the

different mechanisms of action and treatment approaches involved in these disorders, one of skill in the art would not be motivated to look to Yoshimura *et al.*'s teaching regarding the treatment of interstitial cystitis for potential treatments for overactive bladder. Even if one of skill in the art would have been motivated to use ω-conotoxin as described in the Maggi *et al.* reference instead of NO or an NO precursor as described in the Yoshimura *et al.* reference, such a motivation would have been driven by a desire to seek a treatment for interstitial cystitis and not the presently claimed method of treating overactive bladder. Accordingly, one of skill in the art would not have been motivated to combine the teaching of the Yoshimura *et al.* reference with that of the Maggi *et al.* reference to arrive at the presently claimed treatment for overactive bladder using orally administered ziconotide.

In addition to a motivation to combine, a *prima facie* case of obviousness requires that one of ordinary skill in the art would have expected the teachings of the cited references to be successful. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200; 18 USPQ2d 1016 (Fed. Cir. 1991). It is Applicants' contention that the combination of the Maggi *et al.* and Yoshimura *et al.* references fails to provide the required expectation of success with respect to treatments for overactive bladder.

First, as described above, interstitial cystitis as described by Yoshimura *et al.* and overactive bladder as presently claimed are mechanistically different and are traditionally treated with drugs targeting these different mechanistic causes. One of skill in the art therefore would not have a reasonable expectation of success that a treatment disclosed for interstitial cystitis, such as NO or an NO precursor as described in the Yoshimura *et al.* reference, would show efficacy in the treatment of overactive bladder. One of skill would have even less of an expectation of success if the disclosed methods of treatment were modified to substitute another agent, such as the substitution of NO or an NO precursor as described in the Yoshimura *et al.* reference with a ω-conotoxin as described in the Maggi *et al.* reference. Therefore, the combination of the Maggi *et al.* and Yoshimura *et al.* references fails to teach with any probability of success that an orally administered ω-conotoxin would be useful in the treatment of overactive bladder.

Second, the Yoshimura *et al.* reference provides different and contradictory teachings with respect to the effects of NO on the bladder. For example, in one passage, the authors state that "NO is also proposed as a mediator that suppresses tissue inflammation or injury in visceral organs such as intestine and bladder ... production of NO in the bladder is decreased in patients with interstitial cystitis ... and that orally administered L-arginine, an NO precursor, was effective in reducing irritable symptoms in these patients" (see page 310, second column, lines 17-27 of Yoshimura *et al.*). However, the authors also state that "chronic bladder inflammation upregulates the expression of NOS [nitric oxide synthase] in bladder afferent neurons ... [and] suppression of NO release in the spinal cord by a NOS inhibitor suppressed cystitis-induced bladder hyperactivity ... [t]hus it seems likely that increased generation of NO in afferent nerve terminals in the spinal cord may be involved in enhancing reflex activity and/or inflammatory responses in the bladder" (see page 310, second column, lines 8-16 of Yoshimura *et al.*). This led the authors to conclude that "it is reasonable to assume that NO has a dual effect, possibly dependent on concentration or different sites of action (i.e., central or peripheral), to suppress or amplify nociceptive mechanisms" (see page 310, second column, lines 31-35 of Yoshimura *et al.*).

Thus, the Yoshimura *et al.* reference itself teaches that the effect of NO on bladder activity is unpredictable. Accordingly, one of skill in the art would not even have a reasonable expectation of success that NO or an NO precursor as described in the Yoshimura *et al.* reference would show the same efficacy in the hands of another for the treatment a given urinary tract disorder due to idiosyncrasies associated with route of administration and site of action of the drug. Such uncertainty exacerbates the lack of expectation of success described above with respect to the use of NO or an NO precursor to treat such mechanistically different disorders such as interstitial cystitis and overactive bladder, let alone the substitution of NO or an NO precursor as described in the Yoshimura *et al.* reference with a ω-conotoxin as described in the Maggi *et al.* reference. Therefore, the combination of the Maggi *et al.* and Yoshimura *et al.* references fails to teach with any probability of success that an orally administered ω-conotoxin would be useful in the treatment of overactive bladder.

In summary, one of skill in the art would not be motivated to combine the Maggi *et al.* and Yoshimura *et al.* references to arrive at the claimed method. Furthermore, one of skill in the art would not have a reasonable expectation of success based on the Maggi *et al.* and Yoshimura *et al.* references, alone or in combination, that an orally administered ω-conotoxin would be useful in the treatment of overactive bladder. Accordingly, the rejection under 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §103(a) is overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required. However, in the event that extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Date of Deposit February 27, 2006

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